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Visually Clean and Visual Limits

Last month I discussed the application of statistics for determining a visual limit. This month we will consider another issue related to what the PIC/S regulatory document (PIC/S PI 006-03) states about visual limits.

First, let's clarify the purpose of a visual limit (VL) determination. VL is typically expressed in units of mass per surface area, such as $\mu g/cm^2$.The purpose is to define a level at which a defined residue is clearly visible on a defined surface (typically a certain material of construction and surface roughness) under defined viewing conditions (typically distance, lighting and angle). The VL is then used to in this way: If the same surface is viewed under identical or more stringent viewing conditions and is visually clean, then the residue is present at a level below the VL. If the VL is equal to or below the limit established by a carryover calculation in a cleaning validation protocol, then the viewed surface meets the defined acceptance criterion without the need to perform swab sampling.

The relevant section in PIC/S PI 006-03 is section 7.11.3, which states:

> Carry-over of product residues should meet defined criteria, for example the most stringent of the following three criteria:
> (a) No more than 0.1% of the normal therapeutic dose of any product will appear in the maximum daily dose of the following product,
> (b) No more than 10 ppm of any product will appear in another product,
> (c) No quantity of residue should be visible on the equipment after cleaning procedures are performed. *Spiking studies should determine the concentration at which most active ingredients are visible* [emphasis added]

The question that we will address is whether for *any* use of a visually clean criterion, must I do spiking studies to determine the VL? In other words, most people agree that if I am using visually clean alone without any swab or rinse sampling for that surface, then I should do spiking studies to determine what the VL is. While it is commonly stated that visual limits are on the order of 1-4 $\mu g/cm^2$, we all realize this is variable. And, if the calculated carryover limit is 0.1 $\mu g/cm^2$, it is not likely that I will be able to use visually clean alone. Furthermore, if the calculated limit is above a certain value (which will depend on the viewing conditions utilized), I would make the case that spiking studies are not required. For example, if the carryover limit were 13.5 $\mu g/cm^2$ and a stainless steel surface could be viewed in a short distance (such as 2 feet) under reasonable lighting conditions, I would make case that the VL would be significantly below the calculated limit and spiking studies were not needed. Obviously, some kind of reasonableness needs to be used for this latter case; it might not apply if it were a white residue on a PTFE surface.

But the key question for this Cleaning Memo is whether I should (or am required to) determine the visual limit (by performing spiking studies) if I am only using visual examination to *supplement* swab and/or rinse sampling for the same examined surface.

There are at least two possible interpretations of the "recommendation" in PI 006-03 in Section 7.11.3.c that "Spiking studies should determine the concentration at which most active ingredients are visible". One

interpretation is that this requirement must be read in context, and that context comes from the phrase "the most stringent of the following three criteria". That is, the requirement for spiking studies only applies if visually clean is the most stringent of the three criteria. If this is the case (and this is my interpretation), then current industry practices are generally consistent with this interpretation.

A second interpretation is that I must perform spiking studies (to determine the VL) for *all* cases where I use visually clean as a criterion in a cleaning validation protocol. Does this interpretation make scientific sense? Is there a scientific rationale why this should be done in all cases, and in specific where visual examination is done to supplement swab and/or rinse sampling? Let's see what value it adds in the latter situation. To consider that, we'll take a look at several examples.

Let's suppose for the first example that we are in a situation where the calculated limit for a residue is below the visual limit. For example, suppose the calculated carryover limit is 1 $\mu g/cm^2$ and the VL (if I were to do spiking studies) is 3 $\mu g/cm^2$. In my cleaning validation protocol, I measure residues for a given surface by swabbing and get results below 1 $\mu g/cm^2$. In addition, equipment is visually clean. I pass both those acceptance criteria. But, would a spiking study to actually determine the value of VL make any difference in whether I pass or fail. Yes, it might be "nice to know" that the VL for the residue is actually 3 $\mu g/cm^2$, but is it necessary? My answer is "No".

For this same example (the calculated limit for a residue is below the visual limit), let's suppose that when I measure residues by swabbing the results are below 1 μg/cm2. But, my visual examination shows that the equipment is not visually clean. With those results, I would fail my protocol. Obviously it should be clear that the visual failure is not caused by the target residue (for example, the active), because I have analytical data showing that the active is at an acceptable level. The visual failure is most likely caused by other residues (such excipients and/or cleaning agents). Again, knowing a specific VL for the active offers no additional information or benefit.

There are two other situations in this same example (the calculated limit for a residue is below the visual limit). One is where the swab analytical data is above the acceptance limit and the equipment is visually clean. Another is where the swab analytical data is above the acceptance limit and the equipment is not visually clean. I won't go into detail, for these two cases, but it should be clear in these situation that spiking studies to determine a value for the VL offers no value.

These last three paragraphs have dealt with the example where the calculated limit for a residue is below the visual limit. Now we'll consider the *reverse* situation, where the calculated limit for a residue is above the visual limit. For example, suppose the calculated carryover limit is 5 $\mu g/cm^2$ and the VL (if I were to do spiking studies) is 3 $\mu g/cm^2$. In my cleaning validation protocol, I measure residues for a given surface by swabbing and get results below 5 $\mu g/cm^2$, and the equipment is visually clean. Does the fact that I have an experimentally determined VL add anything? Well, you might say that if I did a spiking study, I would know that the amount of the active was below 3 $\mu g/cm^2$. But what is the value of knowing that? If for some reason, I measured the residue by swabbing and the result was 4 $\mu g/cm^2$ (thus meeting the analytical limit), then if the VL was 3 $\mu g/cm^2$, I would fail the visually clean criterion even though I did not perform a spiking study to determine the VL. In this case, it is not possible to have a situation in which I failed the analytical swabbing limit but passed the visual limit.

To sum it up, in these examples (where I am both measuring the residue by swabbing to compare it to the calculated carryover limit and determining the equipment is visually clean), it is not the case that determining the VL by spiking studies adds any significant benefit to confirming that the sampled surfaces are acceptably clean.

Some of you might be thinking, “Okay, but what about using visually clean as a monitoring technique after the validation runs (the qualification runs) are complete. Shouldn't I perform a VL in that case?” And that is a good point which we will address in next month's Cleaning Memo.